AMENDMENTS TO THE SPECIFICATION:

On page 1, after the title, please insert the following new paragraph as follows:

This application is a National Stage Application of PCT/JP2004/014377, filed September 30, 2004.

Please amend paragraph [0001] as follows:

[0001] The present invention relates to a method for inhibiting the degradation of at least one of CREBL1 (cAMP responsive element binding protein-like 1), ATF6 (activating transcription factor 6), and HNF-4α (hepatocyte nuclear factor 4α), and a method for preventing and/or treating diabetes, comprising inhibiting the degradation by HtrA2 (high temperature requirement protein A2) of at least one of CREBL1, ATF6, and HNF-4α. Particularly, the present invention relates to a method for inhibiting the degradation of at least one of CREBL1, ATF6, and HNF-4α, comprising inhibiting the function of HtrA2 (for example, inhibiting the cleavage by HtrA2 of at least one of CREBL1, ATF6, and HNF-4α or inhibiting the interaction of at least one of CREBL1, ATF6, and HNF-4α with HtrA2). Further, the present invention relates to a method for preventing and/or treating diabetes comprising using the aforementioned degradation inhibition method. Further, the present invention relates to a method for preventing and/or treating diabetes comprising using one or more compounds that inhibit the degradation by HtrA2 of at least one of CREBL1, ATF6, and HNF-4α, and an agent for preventing and/or treating diabetes comprising one or more compounds. Further, the present invention relates to a method of identifying a compound that inhibits the degradation of at least one of CREBL1, ATF6, and HNF-4α. Further, the present invention relates to a method of identifying a compound that is to be an active ingredient for an agent for preventing and/or treating diabetes. Further, the present

invention relates to a method for inhibiting cell death comprising inhibiting the degradation by HtrA2 of CREBL1 and/or ATF6. Further, the present invention relates to a method for inhibiting cell death comprising using one or more compounds that inhibit the degradation by HtrA2 of CREBL1 and/or ATF6, and to an agent for inhibiting cell death comprising one or more compounds. Further, the present invention relates to a method for preventing and/or treating type 2 diabetes comprising inhibiting the degradation by HtrA2 of HNF-4α. Further, the present invention relates to an agent for preventing and/or treating type 2 diabetes comprising one or more compounds that inhibit the degradation by HtrA2 of HNF-4α. Further, the present invention relates to a reagent kit comprising at least one selected from the group consisting of HtrA2, a polynucleotide encoding HtrA2, and a vector containing the polynucleotide encoding HtrA2; and at least one selected from the group consisting of CREBL1, ATF6, HNF-4α, a polynucleotide encoding CREBL1, ATF6, or HNF-4α, and a vector containing the polynucleotide encoding CREBL1, ATF6, or HNF-4α.

Please amend paragraph [0038] as follows:

[0038] Fig. 4 shows that the degradation of CREBL1 by active HtrA2 (mature HtrA2) was detected in the study using N-terminal tagged-CREBL1 with biotinylated lysine residue within the protein by detecting the Tag ligated at the N-terminal. The band of N-terminal tagged-CREBL1 was reduced significantly with the reaction of active HtrA2 with CREBL1 for 4 hours (4h) or overnight (O/N). The band around 50 kDa that was detected in the study shown in Fig. 3, which is considered to be a band indicating the degradation product of CREBL1, was not detected. The detection was conducted using anti-Tag antibody. On the other hand, the

degradation of CREBL1 by inactive HtrA2 (mature HtrA2 (S306A)) was not observed (Example 4).

Fig. 5 shows that ~~CREBL1~~ HNF4α was degraded in vitro by active HtrA2 (mature HtrA2). The band of ~~CREBL1~~ HNF4α was significantly reduced with the reaction of active HtrA2 with ~~CREBL1~~ HNF4α for overnight (O/N). On the other hand, the degradation of ~~CREBL1~~ HNF4α by inactive HtrA2 (mature HtrA2 (S306A)) was not observed (Example 6).

Fig. 6 shows that ~~CREBL1~~ HNF4α was degraded in a cell by active HtrA2 mutant (mature HtrA2 (ΔAVPS) that lacks N-terminal four amino acid residues of the active HtrA2 (mature HtrA2); or mature HtrA2 (GVPS) with the substitution of alanine at the N-terminal amino acid of the active HtrA2 with glycine). In the analysis using cells in which the mature HtrA2 (ΔAVPS) or the mature HtrA2 (GVPS) was co-expressed with ~~CREBL1~~ HNF4α, the band of ~~CREBL1~~ HNF4α was reduced significantly. On the other hand, in the analysis using cells in which inactive HtrA2 mutant (the mature HtrA2 S306 (ΔAVPS) or the mature HtrA2 S306 (GVPS)) was co-expressed with ~~CREBL1~~ HNF4α, reduction of the band of ~~CREBL1~~ HNF4α was not observed (Example 7).

Please amend paragraph [0062] as follows:

[0062] HtrA2, CREBL1, and ATF6 are known proteins and disclosed in GenBank with the accession numbers NM_013247, ~~NM_00438~~ NM_004381, and NM_007348, respectively. Further, HNF-4α is also a known protein and disclosed in the Swiss-Prot database with the accession number P41235 (registered gene name is HNF4A).

Please amend paragraph [0063] as follows:

[0063] The amino acid sequence of HtrA2 used in the Examples is shown in SEQ ID NO: 4. The nucleotide sequence of HtrA2 DNA encoding the amino acid sequence set forth in SEQ ID NO: 4 is shown in SEQ ID NO: 3. The polypeptide shown by the amino acid sequence set forth in SEQ ID NO: 4 is a mature HtrA2. The mature HtrA2 denotes a mature protein that is generated from HtrA2 precursor protein (SEQ ID NO: 2) by cleavage of its N-terminal 133 amino acid residues and has a protease activity. Hereinafter, the HtrA2 with protease activity may be referred to as an active HtrA2. Further, a protein (SEQ ID NO: 8, which may be referred to as mature HtrA2 (ΔAVPS)) that lacks the N-terminal four amino acid residues (AVPS) in the mature HtrA2, or a protein (SEQ ID NO: 10, in some cases referred to as mature HtrA2 (GVPS)) with the substitution of alanine among the N-terminal four amino acid residues of the mature HtrA2 with glycine may be used as active HtrA2. Such HtrA2 with an introduced mutation can be used as active HtrA2 since there is no change in the protease activity. In the meantime, HtrA2 without protease activity may be in some cases referred to as inactive HtrA2. The inactive HtrA2 may be, for example, HtrA2 mutant without protease activity resulting from a mutation of the amino acid residue that is present at the site necessary for protease activity of HtrA2 in the amino acid sequence of HtrA2. The site necessary for protease activity of HtrA2 has a protease activity domain, more preferably the 174th serine residue of mature HtrA2 (SEQ ID NO: 4) (which is corresponding to the 306th residue of the precursor protein (SEQ ID NO: 2)). More specifically, the inactive HtrA2 may be, for example, HtrA2 mutant (SEQ ID NO: 6, which may be referred to as mature HtrA2 (S306A)) with a substitution of the 174th serine residue of mature HtrA2 (which is corresponding to the 306th residue of the precursor protein (SEQ ID NO: 2)) with alanine. Further, a protein (SEQ ID NO: 12, in some cases referred to as mature HtrA2 (S306A, ΔAVPS))

that lacks the N-terminal four amino acid residues (AVPS) in the mature HtrA2 (S306A), or a protein (SEQ ID NO: 14, in some cases referred to as mature HtrA2 (S306A, GVPS)) with the substitution of alanine among the N-terminal amino four amino acid residues of the mature HtrA2 (S306A) with glycine may be used as inactive HtrA2.

Please amend paragraph [0064] as follows:

[0064] The amino acid sequence of CREBL1 used in the Examples is shown in SEQ ID NO: 16. Furthermore, the nucleotide sequence of CREBL1 DNA encoding the amino acid sequence set forth in SEQ ID NO: 16 is shown in SEQ ID NO: 15. It was found that the nucleotide sequence set forth in SEQ ID NO: 15 had a difference in one nucleotide compared with the known nucleotide sequence of CREBL1 with accession number ~~NM_00438~~ NM_004381 (see Example 2).

Please amend paragraph [0108] as follows:

[0108] Then, CREBL1 gene was amplified by PCR and cloned into pCR-BluntII-TOPO vector. The PCR was carried out using the CREBL1 gene cloned into pCMV-Tag 5 as a template, ATF6-NF1 primer (with BamHI site instead of ATG, SEQ ID NO: 25), ATF6-NR1 primer (with XhoI site following to termination codon, SEQ ID NO: 26), and KOD-plus as DNA polymerase. The nucleotide sequence was determined by the sequencer. It was found that the nucleotide sequence obtained in this example had a difference in one nucleotide (T450C) compared with the nucleotide sequence of CREBL1 that had already been registered in GenBank with accession number ~~NM_00438~~ NM_004381. There is no change in the amino acid resulting from this difference. In the meantime, the termination codon was changed from TGA to TAA. It

was confirmed that these differences were not due to PCR errors. The nucleotide sequence of CREBL1 DNA obtained in this example and the amino acid sequence encoded by the DNA are shown in SEQ ID NO: 15 and SEQ ID NO: 16, respectively. Animal cell expression plasmid for CREBL1 was prepared by digesting the cloned CREBL1 gene with BamHI and XhoI, and then integrated it into pCMV-Tag 3.

Please amend paragraph [0110] as follows:

[0110] In order to integrate ATF6 gene into animal cell expression vector, ATF6 gene was amplified by PCR using the aforementioned ATF6 gene having been cloned into pCR4Blunt-TOPO vector as a template, using ATF6F2L primer (with BglII site immediately before ATG, SEQ ID NO: 31), ATF6R1L primer (SEQ ID NO: 30), and KOD-plus as DNA polymerase, and then cloned into pCR4Blunt-TOPO vector. The nucleotide sequence was determined by sequencer (SEQ ID NO: ~~19~~ 17). ATF6 gene thus cloned was digested by BglII and XhoI to integrate into animal cell expression vector, pCMV-Tag3, digested with BamHI and XhoI.